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Comprehensive studies have been conducted to determine seroreactivity of HIV infected individuals to well defined epitopes on the virus envelope. These have included regions which serve as targets for neutralizations and ADCC mediating antibodies. The principal neutralizing domain (PND) of HIV lies within the third hypervariable domain and is represented by a disulfide linked loop (residues 303-337). This region contains both variable and conserved epitopes. The ADCC targets are present in both gp120 and gp41 and are represented by conserved domains.

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FOREWORD

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The goals of the contract were to identify, map and characterize important target epitopes on the envelope of HIV. We have been successful in identifying four of these although a number of others have been studied. Reference is made to Figure 1 which is a reasonably up-to-date road map of the HIV envelope drawn from the work of many laboratories.

Our specific contributions to this were:

1) Identification of the dominant neutralizing epitope of HIV gp120 (AA 303-337).

2) Identification of two ADCC sites in gp120 (AA 315-329 and 474-518).

3) Identification of a dominant ADCC site in gp41 (AA 644-663).

In brief, the dominant neutralizing epitope, often referred to as V3 and more recently as the principle neutralizing determinant (PND), has been characterized extensively by us and a host of other laboratories. This site is now considered to represent region of the virus which is essential for infectivity and operates at a step post-binding of the exterior glycoprotein to CD4. It is believed to be intimately involved in virus penetration in relation to the fusion process. Our specific contributions to this process are as follows:

1) Immunodominant epitopes in the HIV outer envelope were identified (7) as well as the notion that HIV contained a dominant neutralization site (8). Using three independent approaches, the epitope responsible was finely mapped to the V3 loop (9,10,11).

2) Subsequently, a number of studies were conducted to maximize the immunogenicity of this region including its linkage to a T-cell epitope of gp120 (12). This construct forms the basis of a vaccine candidate described in this application.

3) The mechanism of virus neutralization via this epitope was demonstrated to occur at a step post binding of the virus to the CD4 receptor and closely linked to the fusion process (13).

4) The variability of this region among natural HIV isolates has been extensively studied (14). From this and other work, the notion of the prevalence of viruses resembling the MN isolate was established.

These findings raise the possibility that natural HIV isolates can be grouped into neutralization families, whereby a cocktail of representative V3 domains could be used to induce broadly cross neutralizing antibodies.

5) More in depth analysis of sub-regions of the V3 loop has identified conserved domains which when separated from the variable regions can themselves induce antibodies which neutralize divergent isolates (15). Such more universal epitopes will make the cocktail approach likelier to achieve.

6) Studies have been performed to better define the role of the V3 loop in the process of virus infection and target cell specificity. Using site directed mutagenesis of infectious HIV clones, the critical role of certain amino acid residues in the conserved loop crown has been established (16).

The biological role of this domain continues to grow in importance as antibodies to have recently been implicated as the best correlate for vaccine protection of chimps against HIV infection and as possible deterrents against mother/infant transmission of the virus in humans.

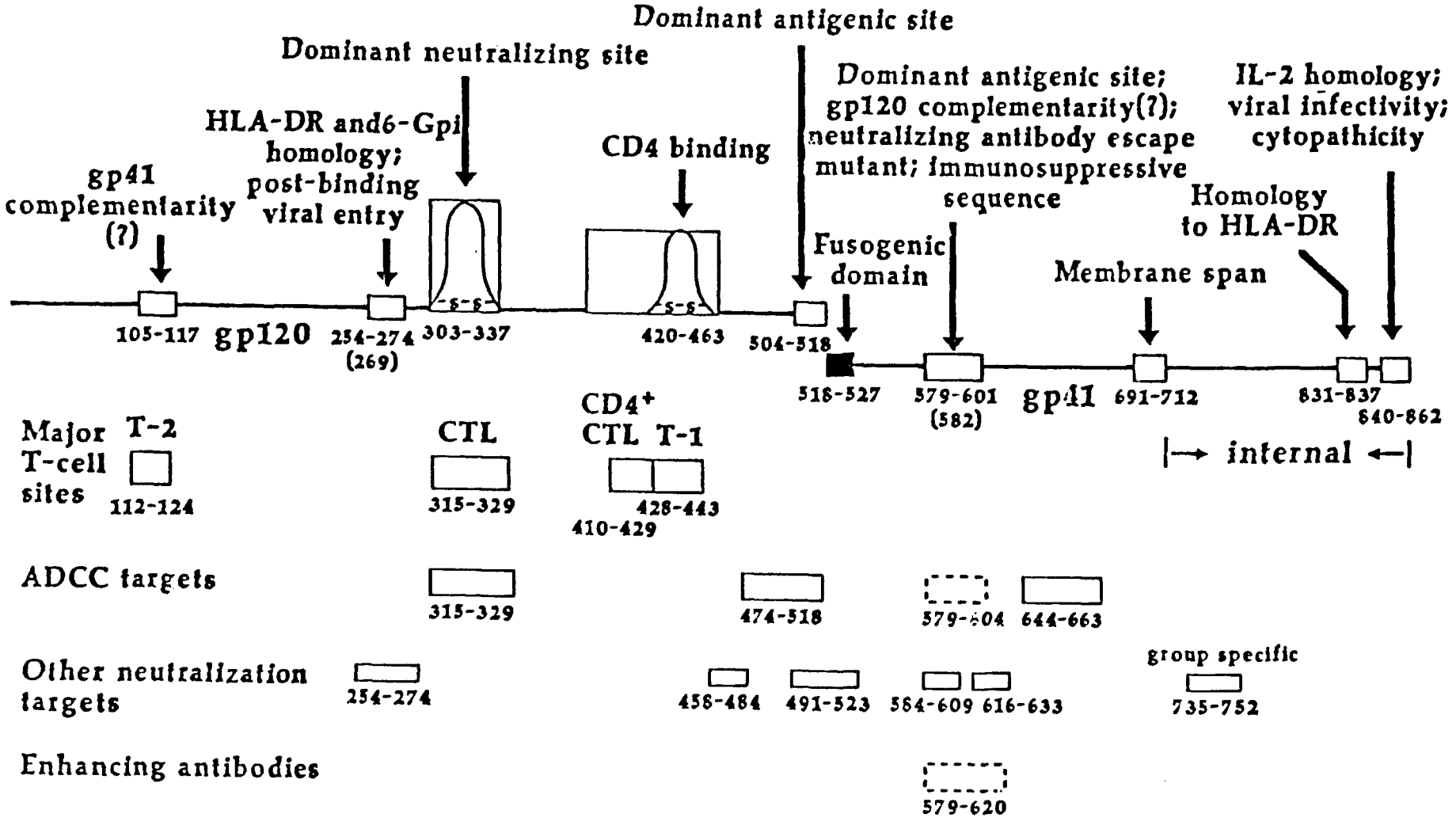
We have also contributed extensively to the understanding of the phenomenon of ADCC as it relates to HIV:

1) The phenomenon of ADCC as it applies to the HIV envelope was originally described (1). Subsequently, the correlates of this defense mechanism with disease progression were defined (2). More recently, the intimate details of the components of this unique phenomenon have been identified (3,4) as well as the fine specificity of ADCC epitopes on HIV envelope (5). This work, in aggregate, has spawned a clinical trial which is in progress (6).

Throughout the course of these studies, a number of important biological systems were also developed and paired with sensitive and specific assays designed to study various properties of HIV and the immune responses to it (7,8,9,10,15,17).

FIGURE 1

Selected Functional and Immunogenic Sites of the HIV-1 Envelope



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